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Reflections in Mutation Research

Hormesis: changing view of the dose-response, a personal account of the history and current status☆

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Abstract

This paper provides a personal account of the history of the hormesis concept, and of the role of the dose response in toxicology and pharmacology. A careful evaluation of the toxicology and pharmacology literatures suggests that the biphasic dose response that characterizes hormesis may be much more widespread than is commonly recognized, and may come to rival our currently favored ideas about toxicological dose responses confined to the linear and threshold representations used in risk assessment. Although hormesis-like biphasic dose responses were already well-established in chemical and radiation toxicology by the early decades of the 20th century, they were all but expunged from mainstream toxicology in the 1930s. The reasons may be found in a complex set of unrelated problems of which difficulties in replication of low-dose stimulatory responses resulting from poor study designs, greater societal interest in high-dose effects, linking of the concept of hormesis to the practice of homeopathy, and perhaps most crucially a complete lack of strong leadership to advocate its acceptance in the right circles. I believe that if hormesis achieves widespread recognition as a valid and valuable interpretation of dose-response results, we would expect an increase in the breadth of evaluations of the dose-response relationship which could be of great value in hazard and risk assessment as well as in future approaches to drug development and/or chemotherapeutics.
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1. Introduction

This article is concerned with a phenomenon that has come to be known as hormesis. Hormesis is a dose-response phenomenon which is characterized by a counterintuitive switchover from low-dose stimulation to high-dose inhibition that is not infrequently encountered in the course of a toxicity assay. The story begins with a scene-setting recapitulation of the discovery and early development of the hormesis concept, followed by an attempt to place names, dates, places and concepts into an integrative and insightful whole so as to introduce and analyze an important area of research whose potential significance for toxicology (and especially for risk assessors) is seriously underappreciated in the wider scientific community.

For all practical purposes, the story of hormesis is one of the efforts of numerous investigators who have been striving for decades to enhance our knowledge

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of the various factors that influence the dose-response relationship, the keystone in all of toxicology. In the unfolding of this reconstruction what will emerge most clearly, and perhaps surprisingly, is that even though the linear and threshold dose-response models are the twin pillars of toxicology from which researchers and regulators have derived so much academic/institutional guidance for so many years, they do not reflect the most fundamental toxicological model, which is the hormesis model. This is a type of whodunit review in which I provide my version of how, when, and why early workers in the field of toxicology made a mistake of historic proportions on what the most fundamental nature of the shape of the dose response should be, then discuss why multiple generations of toxicologists have continued to perpetuate this error while imbuing it with an influence that has transformed essentially all US and international estimates of the risks of chemicals and radiation. This story is not pretty, but it should be told.

2. The hormesis concept: the early years

The story of hormesis began about 60 years before it acquired its present name[1] in the obscure and ill-equipped laboratory of Prof. Hugo Schulz at the University of Greifswald in Northern Germany [1–5]. The scene was the early 1880s, when Joseph Lister, Louis Pasteur and Robert Koch were busy setting Europe on fire with their many important discoveries on the causes of infectious diseases and how they might be prevented. Schulz became interested in testing how a medicine long used to treat a form of gastroenteritis might work. He noted that research had recently determined the causative bacterial agent and how to culture it. So he grew the bacteria and exposed them to various doses of the medicine. To his surprise, the medicine had no effect on the microbe, regardless of dose. This led Schulz to a hasty, and possibly erroneous, conclusion that the chemotherapeutic agent acted on the human body by enhancing natural adaptive responses rather than by attacking the microbe more directly. This interpretation gave him a profound appreciation for the medical practice of homeopathy.

Independently of this initial study, Schulz assessed the effects of numerous bactericidal agents, including mercury and phenol, on yeast metabolism. He found that most agents appeared to stimulate metabolism at low concentrations only to inhibit them at higher concentrations. At this point Schulz believed he had found a toxicological explanation for his developing homeopathic beliefs. As a result of the publicity following these initial studies he became the main academic hero for numerous advocates of homeopathy, and thus the theory of hormesis was born in close association with homeopathy as a preventive/therapeutic modality.

Homeopathy has long been an embattled approach to medical practice, and Schulz's decision to embrace homeopathy may well have ensured that his career remained in Greifswald rather than in some closer association with Koch, from whose lab three of the first seven Nobel Prize winners in biology and medicine would later be drawn. Nonetheless, Schulz's work did attract a fair amount of attention, and was confirmed by a few and extended by many. The possibility that his findings were of general significance occurred to a number of people, and the biphasic response was encountered in a variety of other organisms, including several species each of bacteria and plants. Interestingly, soon after Ferdinand Hueppe, a protege of Koch and the author of a highly regarded text on bacteriology in 1896, claimed to have confirmed Schulz's biphasic phenomenon in bacteria, he began to argue with considerable passion that this concept should not be rejected simply because of Schulz's close association with homeopathy. Interestingly, the concept of low-dose stimulation/high-dose inhibition, as seen initially in the work of Schulz and subsequently in that of Hueppe, soon became known as Hueppe's Rule, primarily one supposes because the latter had the prestige of Koch's lab even though scientific primacy belonged to the more marginalized Schulz. This situation changed shortly afterwards, however, when Grote and Schulz [7] published their 1912 book on biphasic responses in which they gave credit and esteem to the reputation of their deceased colleague, the homeopath physician, Rudolph Arndt, for his role in galvanizing Schulz's attention to the issue as well as his role in the process of concept development. As a result, the phenomenon that was to

[1] Hormesis was given its name by Southam and Ehrlich [6], who had been studying the effects of red cedar extracts on fungi and were reporting the unusual biphasic dose-response curves that they kept seeing when they plotted their results.

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become known by a great many people as hormesis soon became known as the Arndt–Schulz law.[2]

Interest in the effects of low doses rapidly expanded especially with many studies of interactions involving (mainly) plants, bacteria and fungi, most notably in Europe, the US and Japan. Convincing findings were reported by outstanding turn-of-the-century researchers at leading universities in the US, including Cornell (Benjamin Duggar, later to be a mentor of Alexander Hollaender at the University of Wisconsin), Wisconsin (Louis Kahlenberg, former student of Wilhem Ostwald, Nobel Laureate), Illinois (F.L. Stevens), Columbia (C.O. Townsend, H.M. Richards), and Stanford (G.H. Jensen) and many others [2,3]. These studies were mostly well designed and executed, and carefully interpreted. Their emphasis on plant, bacterial and fungal systems enabled early investigators to make use of the larger numbers of doses that are so important if one wishes to describe the biological effects at low concentrations that are now known as hormesis. Similar findings were made by outstanding European scientists, one of whom (Charles Richet) was later to receive the Nobel Prize for his study of anaphylaxis. It is important to note that none of these reports of stimulation at low doses and inhibition at higher doses were either controversial or linked to any particular ideology. In the US, this research was not closely linked to homeopathy but rather was seen as principally a scientific question. Of particular note was the Yale Prof. Charles Winslow, the Editor-in-Chief of the *Journal of Bacteriology*, who directed the students responsible for numerous dissertations in the 1920s through the mid 1930s that explored the occurrence of biphasic dose responses and their mechanistic framework. Thus, as the chemically oriented toxicology community was approaching the mid 1930s, the concept that was to become hormesis was part of the mainstream of scientific investigation and had the support of an impressive line-up of investigators.

[2] Note: our analysis of the concept of hormesis and its supportive data has resulted in our distinguishing between hormesis and the Arndt–Schulz law. The Arndt–Schulz law assumed a direct stimulation at low doses followed by an inhibition at higher doses. Our concept of hormesis incorporates two forms of stimulation; one is a direct one that could be similar to that of the Arndt–Schulz law, while a second stimulation may result from overcompensation to an initial disruption in homeostasis.

On a parallel track, but with a nearly two decade handicap (since X-rays and radionuclides had not been discovered until the mid 1890s) an impressive array of investigators was making similar claims of low-dose stimulation/high-dose inhibition by radiation mostly in plants, fungi, insects, but also in clinical practice [3–5]. While these findings were less extensive than those already reported in the chemical literature, they were sufficient to have done justice to most other similar scientific hypotheses during that era. However, something happened during the 1930s to both concepts (i.e. chemical and radiation hormesis) that was to result in the hormetic concept becoming marginalized—and remaining there until the present time.

How could two viable hypotheses that had such an impressive start and that had clearly established a scientific beachhead simply melt away to near irrelevancy in an earlier version of "cold fusion"? The causes are many and interacting, with hormesis being the innocent victim of inherent theoretical limitations and societal priorities as well as external enemies and a lack of scientific leadership. A most difficult problem inherent to hormesis is that the low-dose stimulation that occurs is modest; this makes it difficult to replicate. Societal interest during the early decades of the 20th century was also more focused on high-dose effects, such as ensuring the killing of bacteria and insects, or on reducing the exposure of industrial workers to relatively high doses of toxic agents, than on looking for modest low-dose stimulatory responses of uncertain significance.

In the radiation field, hormesis came to be greatly exaggerated by proselytizers, who oversold what radiation hormesis could never have delivered. For example, chemicals, such as radium were portrayed as the next elixir, or as effective plant fertilizers [3–5]. When the hormetic concept miserably failed to satisfy on these accounts, interest dried up quickly and more serious observers concentrated on assessing adverse health effects at higher doses. In addition, the internationally famous A.J. Clark of the University of Edinburgh took aim at the Arndt–Schulz law, directing a fierce and unrelenting attack on it in his acclaimed *Handbook of Experimental Pharmacology* [8]. Thus, there was a combination of being difficult to prove, a subject of oversold promises, an obvious linkage to homeopathy, governmental concern with high-dose effects, ineffective scientific leadership and prestigious

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opponents; all of this proved too much for hormesis to overcome. By the end of the 1930s, it was a marginalized concept.

3. Hormesis—a renewed interest

Over the next 60 years, the hormetic hypothesis had several minor resurgences, only to go back to having essentially negligible name recognition and influence. However, a strategic opening for hormesis to undergo a resurgence emerged slowly in the early 1980s as the EPA and other regulatory agencies accepted low-dose linearity modeling to estimate cancer risks and began to use this as a vehicle to answer the "how clean is clean?" question for contaminated sites. Since hormesis implied thresholds for non-carcinogens and carcinogens alike it was thought of as a means with which to confront the low-dose linearity paradigm. In fact, this was the issue motivating the First Conference on Radiation Hormesis in 1985 (see Proceedings in *Health Physics*, 1987) and some of the biological effects of low level exposures (*BELLE*) (see belleonline.com) activities over the past decade.

As an outgrowth of these activities we have been attempting to obtain a better understanding of the nature of the dose-response relationship, especially in the low-dose zone. Our principal motivation was a desire to resolve the long-standing scientific debate (and often ideological feud) over whether the threshold or linear response model should be used as the default assumption in the assessment of carcinogen risk. There did not seem to be an issue for non-carcinogens, given that the threshold response model already had broad acceptance here.

Assessing threshold versus linear models for carcinogens has the potential to bring one in contact with the biphasic-hormetic[3] response model in which responses at low doses are opposite and not proportional to those observed at high doses (Fig. 1).

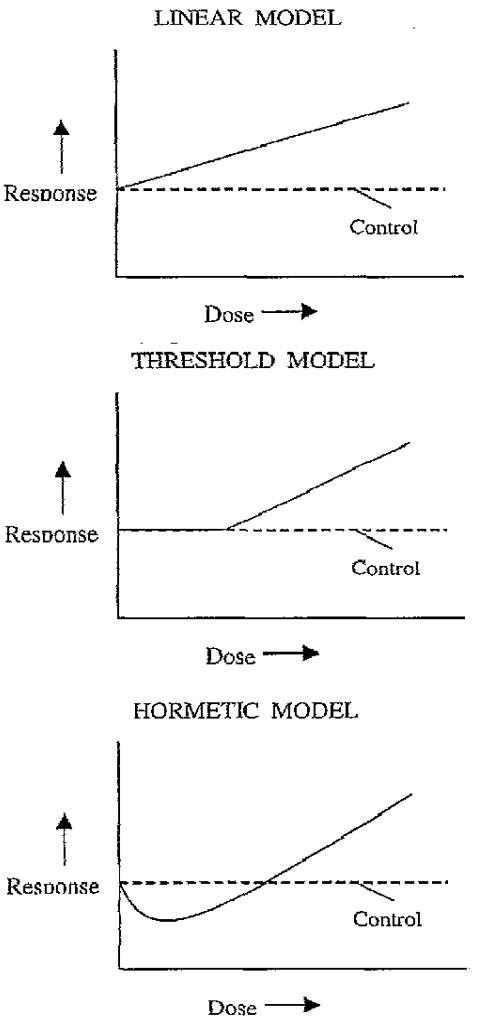

Fig. 1. Stylized curves illustrating the linear, threshold and hormetic dose-response models for carcinogens.

In the case of carcinogens, this generally means that the agent-induced cancer risk disappears with a J-shaped/hormetic curve, with low doses being associated with cancer risks less than controls while at higher doses one expects a dose-dependent carcinogenic effect as normally predicted. The real significance of the hormetic model in the conflict over threshold versus linear response models is of course that if hormesis could be unequivocally demonstrated as universal then it would establish a bona fide thresh-

[3] Definition of hormesis: hormesis is a dose-response phenomenon characterized by a low-dose modest stimulation (e.g. about 30–60% greater than the control at maximum), and a high-dose inhibition. This response appears to result in two ways, either as an overcompensation to a disruption in homeostasis or via a direct stimulation/inhibition response. A detailed article and debate on the definition of hormesis has been recently published [9].

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old for carcinogenic effects. This would immediately discredit the many uses of linearity models to estimate cancer risk at low doses. Thus, the unequivocal demonstration and characterization of hormesis, and its acceptance as the default model in estimating low-dose effects, clearly has the potential to drastically affect cancer risk assessment. In the absence of hormesis it has been extremely difficult to differentiate a linear from a threshold model in the low-dose zone. In such situations, the linear model tends to be adopted, in large measure because the precautionary principle framework is allowed to prevail.

4. Hormesis: establishing documentation

Despite the impetus to resolve the low-dose cancer risk assessment question via the use of the hormetic model, we reasoned that if hormesis is a real phenomenon then it must be evolutionarily based and should therefore be quite broadly distributed across biological systems, working through multiple physiological processes with underlying molecular pathways that should be amenable to analysis. Thus, it made little sense to focus solely on the question of chemical/radiation-induced cancer and its risk assessment, as important as this was. We felt that the question needed to be framed in a broader and more fundamental biological/evolutionary way. Our strategy in assessing hormesis therefore was to establish objective criteria to test whether it existed and was generalizable, as evidenced (for example) by its occurrence independently of biological system, endpoint, or chemical/physical stressor. If all of these criteria were satisfactorily met it would be important to determine the quantitative features of the dose response, investigate its mechanistic foundations, and attempt to understand how these relate to homeostatic regulatory mechanisms. A starting point had to be the development of a definition of hormesis that was toxicologically and statistically based so that an objective and consistent evaluative framework could be generally agreed upon *a priori*.

Although some examples of hormesis were known to exist in the toxicological literature, at the initial stage of our assessment we were not sure if these were relatively rare exceptions (assuming they did not lack adequate replication, statistical power or mechanistic plausibility, as not a few supposed examples clearly did), or whether this phenomenon was more widespread and predictable. If hormesis was to be of widespread significance in the biomedical and toxicological domains it needed the important features of biological centrality. That is, it should be commonly observed, and should be an evolutionary expectation, not an exception.

Our initial strategy was to identify and evaluate possible examples of hormesis from the broad spectrum of biologically based research without restrictions as to system, endpoint or agent tested. We would then apply our own quantitative evaluation methodology to the data for each of the examples we uncovered. As a result of this approach we were able to identify many hundreds of specific examples of hormetic dose responses in various computer databases using a combination of critical key word descriptors, considerable cross referencing, and systematic hand searching/inspection of all articles in more than two dozen journals from their inception to the present. This survey clearly established that hormetic effects are in fact common when experiments have been properly designed to assess dose responses in the low-dose range. In fact, we now have an database of over three thousand examples of the hormesis phenomenon. A detailed evaluation of this database revealed certain important common dose-response features that appeared to be independent of organism, biological system, endpoint or agent tested [10–13].

The low-dose stimulatory responses within the hormetic dose-response curve appear to have a limited amplitude, almost always going no more than a factor of two above the control value. The maximum stimulatory response is more commonly in the 30–60% above control range. Thus, we believe that when a stimulatory response of greater than four-fold is observed it is likely to be a biological phenomenon that is different from hormesis.

The stimulatory dose range for hormetic effects is typically less than a factor of 20-fold immediately below the NOAEL (no observed adverse effect level). This would account for about 70% of the examples so far examined. However, in about 2% of the examples of hormesis examined the stimulatory dose range is in excess of 1000-fold (Fig. 2). While the causes of this potential broad variability in stimulatory range remain to be assessed, we have made some progress in

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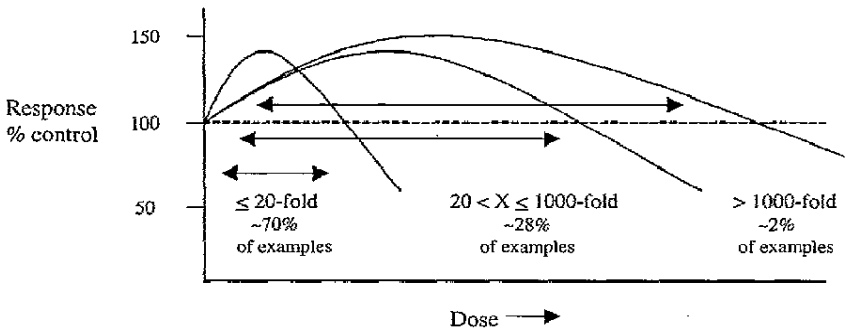

Fig. 2. Stylized dose-response curves reflecting the relative distribution of stimulatory dose ranges. Note: the maximum stimulatory response is usually 130–160% of the control value.

understanding how the range can be modulated. Such an understanding may be important from a risk assessment perspective, but may be even more important from a clinical perspective where dose optimization rather than exposure minimization is the driving force.

By our definition, the hormetic response is always linked to the traditional toxicological NOAEL [9]. That is, the hormetic stimulation is contiguously followed by a transition into the traditional toxic response zone. The linkage of the hormetic response to the toxicological NOAEL is critically important, since it provides a stable frame of reference in relation to risk assessment guideposts and the goals of toxicological testing and assessment. By relating the hormetic response to the dose-response continuum containing the NOAEL, LOAEL (lowest observed adverse effect level), etc. in a predictable and stable manner, risk assessors are able to enhance the flexibility and accuracy of their assessments by permitting the incorporation of the concept of optimization of exposure/response into their methodology. This allows hormesis to achieve a broader recognition as a fundamental and central feature of biological processes. On the theoretical side the linkage of the hormetic stimulation to the NOAEL functionally enjoins it with the concept of homeostasis, a universal concept and phenomenon.

While the initial hormesis database was useful in establishing the biological validity of this concept, it did not provide sufficient insight into the frequency of hormetic responses in the toxicological literature. This was considered a vital step in any meaningful evaluation of the potential biological centrality of hormesis. If hormetic effects were real but occurred in fewer than 1% of properly designed studies, its utility would be rather limited. However, if it were significantly more common (e.g. >30%) then more formal acceptance in testing and assessment procedures would be called for.

In order to estimate the frequency with which hormetic effects could be identified in the toxicological literature we created a second hormesis database. In this evaluation, we screened over 20,000 articles in three toxicological journals covering issues from the mid 1960s to the present [10]. Only 1.5–2.0% of the studies had study designs that were consistent with our rigorous *a priori* entry criteria. Of the dose responses that did satisfy the entry criteria (in practice this means having multiple doses below a toxicologically derived NOAEL plus a clear toxicological dose response at the higher dose levels) approximately 40% were found to satisfy the evaluative criteria, i.e. to display reasonably convincing evidence of hormesis. (If we had relaxed the evaluative criteria to a limited but still fairly demanding level, the frequency would have been well above 50%.) Even more impressive is that the frequency of statistically significant responses for doses below the NOAEL was 32-fold more frequent in the hormetic direction than in the opposite direction. This clearly supports the non-random nature of the below NOAEL responses.

While the frequency and quantitative features of the hormetic dose response are critical to the acceptance of hormesis as a central theorem of toxicology, we also needed to develop a better mechanistic understanding before broader acceptance would be

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forthcoming. Our strategy to address the issue of mechanism was found in the pharmacological, rather than the more traditional toxicological, literature. We needed to know the mechanisms by which biological systems operate a switch from stimulation to inhibition. Although precisely focused dose-response explanatory data are quite rare in toxicology, they are relatively commonplace in pharmacology, and indeed the pharmacological literature provided evidence for hormesis-like dose responses for essentially all receptor systems (e.g. dopamine, prolactin, adrenergic, opiate, adenosine, nitric oxide, various prostaglandins and others) along with mechanistic explanations at least down to the receptor level, and often at even greater depths of understanding. Further investigation revealed that opposing responses were often induced by the same endogenous agonist depending upon differing affinities to receptor subtypes that might lead to either stimulatory or inhibitory pathways [11]. When assessed over a broad dose range the response was typically biphasic with quantitative features like those of chemical and radiation-induced hormesis. Thus, we could now demonstrate the existence of hormesis-like effects in both the toxicological and pharmacological literatures [12–14], provide a reasonable estimate of their frequency over the past three to four decades [10], and confidently account for the biphasic features of the dose-response relationship in essentially all receptor-based systems [11].[4] This remarkable sequence of events over a 5-year period brought us from the initial stage of not knowing whether hormesis existed to a recognition that it is likely to be a central feature of a great many biological systems, potentially with enormous implications for pharmacology, toxicology and medicine. The original question of threshold versus linearity in cancer risk assessment, while obviously still very important, then became secondary to understanding a phenomenon that was of even greater fundamental interest. Nonetheless, our emerging perspective on the generalizability of hormesis ought to be able to contribute to an improved framework in which to envisage the nature of carcinogen dose responses as well as their underlying mechanisms.

[4] Mechanisms underlying changes in the dose response (as in the hormetic biphasic response) are rarely discussed in the toxicological literature, including the chemical and radiation carcinogenesis literatures. The different mechanistic focus between pharmacology and toxicology is an important difference that has been generally under-appreciated.

5. Hormesis and cancer

While much of the motivation that re-invigorated the concept of hormesis is its theoretical potential to change the current cancer risk assessment model it is important to be aware that although the hormesis concept has a long history, it is not that long since the idea that carcinogen dose responses may be U-shaped first emerged. Thus, for example Luckey [15], an ardent supporter of hormesis, did not even discuss the topic of cancer in his first book on radiation hormesis [15] whereas his second (1991) book contains a lengthy discussion of matters relating to cancer [16]. This probably reflects the fact that a number of animal model studies dealing with chemical and radiation carcinogenesis and hormesis were first described in print in the 1980s, while a few similar studies (e.g. [17–24]) were published prior to 1980. However, the concept of hormesis in these studies was ignored by external reviewers and either ignored or de-emphasized by the authors as well. Thus, what might normally have been reported as a striking new finding, was presented as an "observation", never highlighted or discussed. Nonetheless, many of these studies revealed hormetic responses, and suggested that such findings might be observed again if appropriate study designs were employed. More recently, we published two papers in which we specifically discussed chemical [25] and radiation [26] induced cancer and hormesis. In addition to providing numerous examples of hormesis in animal model studies, we also demonstrated that hormetic effects could be observed at a number of stages prior to the development of a tumor, and discussed possible mechanistic hypotheses that could account for the hormetic responses seen in the cancer bioassays.

The detection of hormetic responses presents unique challenges for cancer bioassays. First, it requires that there be a large number of doses, including several below the apparent threshold. Second, it is necessary for the background incidence of tumors to be sufficiently high that hormetic decreases, if they should occur, will definitely be detected. While there are several other complexities that might affect the outcome, selection of the animal/tumor system and the details

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of study design are prominent, and these alone may greatly restrict the numbers of experimental studies from which to assess possible relationships between hormesis and cancer more rigorously. Nonetheless, we believe that a solid core of such studies already exists and is very reliable, thus extending the hormetic hypothesis into the general area of carcinogenesis (see [25,26] for reviews).

6. Final perspectives

While efforts to assess hormesis have been rewarded with unexpected biological insights, it is important to emphasize that however common hormesis is in properly designed experiments, it is not easily studied and is often therefore overlooked or ignored, thereby contributing to its general omission from toxicological text books and its poor recognition and/or acceptance. It is difficult to study primarily because it requires the investigator to use a large number of properly spaced doses, to identify a reliable NOAEL in preliminary experiments, and, frequently, to include a temporal component in some experiments. It also requires typically large sample sizes, mainly because the low-dose stimulation is modest and statistical power issues quickly become critical. Likewise, with modest stimulatory responses it is always possible that chance is a reasonable alternative explanation. Therefore, claims of hormetic responses need to be carefully and multiply replicated to provide evidence of proper causal determination. Thus, the study of hormesis can never be a casual exercise using the same study design rules as will suffice in high-dose toxicity studies. Simply adding an extra dose in the low-dose zone will not allow one to properly test for hormesis. Yet, if a critical long-term goal of toxicology is to better understand how biological systems respond to low levels of environmental stressor agents then the careful assessment of hormesis becomes central and critical. Hormesis is also important since it demonstrates that high- to low-dose extrapolation assumptions used in cancer risk assessment are no longer necessarily adequate in characterizing low-dose risks [27].

Although we have approached the issue of hormesis from a toxicological perspective, researchers from other biological fields may have addressed the same or closely related concepts under the guise of different names, including the following: J-shaped, U-shaped, reverse dose response, opposite effect, overcompensation response, Arndt–Schulz law, Yerkes–Dodson law, bi-directional responses, dual effects, subsidy gradients, intermediate disruption hypothesis and almost certainly others. Regardless of this academic dichotomy as seen through the use of different words for similar concepts, the biological systems that provide such information frequently show hormetic-like dose responses with remarkably similar quantitative features.

Despite its widespread occurrence in diverse biological systems, hormetic responses may not always be observed in properly designed studies focusing on low-dose responses. We have sufficient evidence that this is true, along with adequate mechanistic explanations to account for such exceptions. However, our view is that the biphasic features of the dose response are essential attributes that cells and organisms require to function and survive. Smooth muscles need to either relax or contract, cells must proliferate or not, neutrophils need to be recruited to sites of injury and informed when to stop coming and when to return home. These and numerous other biological regulatory processes are activated by complementary stimulatory and inhibitory pathways that are themselves modulated by agonist concentration gradients that turn on/off biological switches that toxicologists see experimentally as biphasic-hormetic curves.

The concept of the dose response is in an important transition. The issue will no longer be whether the response is a threshold or linear but the role of biological switching (i.e. hormetic mechanisms) in health and disease. I believe that the recognition and knowledge of hormetic responses will bring with it an opportunity to profoundly improve risk assessment, and especially cancer risk assessment, to harmonize the risk assessment of both non-cancer and cancer effects, and to revolutionize approaches to drug development and clinical medicine in which biphasic responses are widely acknowledged, yet where such knowledge is rarely used for patient benefit or the avoidance of harm.

Finally, I return to the opening theme in which I asserted that the concept of hormesis has been systematically ignored by those in the field of toxicology since the late 1930s, as judged by its absence from major texts, or professional society activities (including sessions at annual conferences), and especially perhaps

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as judged by the actions of certain government regulatory agencies which "institutionalized" toxicological concepts, such as the NOAEL and low-dose linearity. Indeed, the whole field of modern toxicology has been built on the twin assumed "facts" of NOAEL and linearity at low doses. This reality directed the field, the questions asked, the projects funded, and the books written, thereby making the marginalization of the hormesis concept solid and even reinforced. It is my feeling that unless toxicologists develop a renewed interest in the concept of hormesis critical progress in many areas will be delayed and the field as a whole will suffer. More important than this, however, is the troubling philosophical question of how a genuine toxicological hypothesis such as hormesis, could have been eliminated from debate in the most open of modern societies.

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